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The Effects of Acutely Increased Ventricular Cavity Pressure on Intrinsic Myocardial Connective Tissue

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Studies of normal hearts have revealed a variety of intrinsic connective tissue structures that surround and interconnect myocytes and ventricular mural layers. Among these structures, springlike coiled perimysial fibers, arrayed parallel to myocytes in the interstitial space, have been described in papillary muscle and ventricle. To evaluate the role of the coiled perimysial fibers under perturbed conditions, rat ventricles were filled with barium-gelatin under different pressures and fixed, and then the myocardium was impregnated with silver to visualize the connective tissue. Ventricles were filled at 30, 70 and 100 to 120 mm Hg.

The coiled perimysial fibers were studied for their orientation, stretch, integrity and relation to sarcomere length. The coils were noted to embed within the fibrous anulus and to knot into an umbilical-like mass at the apex, thus anchoring them at both ends of the ventricle. They underwent focal straightening even at 30 mm Hg, with generalized straightening and disruption at the highest pressure; changes were most pronounced in the midventricle. Sarcomeres were maintained below 2.2 μm at 30 and 70 mm Hg of cavity pressure in regions of coiled perimysial fiber stretch; only with fiber disruption at 100 to 120 mm Hg were sarcomeres significantly lengthened. Other findings included connective tissue disruption between ventricular wall layers that allowed slippage of myocytes and mural thinning.

These observations suggest that coiled perimysial fibers may act as a buffer to protect myocytes from damage under the effects of high cavity pressure.

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Recent and growing interest in intrinsic cardiac connective tissue has led to the identification of multiple structures with well defined organization and orientation in the normal heart. Among these are endomysial and perimysial fibers that surround and interconnect myocytes. It has been observed (1–8) that connective tissue struts extend between the lateral surfaces of myocytes and also attach to other connective tissue structures and blood vessels. Similar struts or strutlike components are also present between groups or fascicles of myocytes and between whole layers of myocardium in the ventricular wall (1–8). Individual myocytes are wrapped in complex pericellular weaves of connective tissue that interconnect with other collagenous components. Running parallel to the long axis of myocytes are both large and small coiled perimysial fibers that look like helically wound springs. These coiled perimysial fibers have been described in papillary muscles (9) and in the ventricular wall (10). They are attached to each other laterally and their network is embedded in fixed fibrous anchor points such as the papillary muscle tendon and the ventricular anulus.

Although there are other large interconnecting fibers surrounding groups of myocytes or whole papillary muscles (1–3,5–7), the role of those connective tissue fibers most intimately associated with myocytes in normal contractile function and in pathologic states remains generally unknown. A functional role for the coiled perimysial fibers has been hypothesized on the basis of their springlike configuration observed in fixed, unloaded ventricles. Thus, they may be important for imparting tensile strength during stretch and for storing contractile energy with subsequent ventricular recoil. Either primary stretch, as might be associated with increased intracavitary pressures, or secondary stretch due to events within the ventricular wall (e.g., ischemia or necrosis) theoretically could alter the geometry, orientation

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and integrity of these and other connective tissue fibers. To evaluate some of these hypotheses, we undertook a study of passive wall stretch in rat hearts under various cavity filling pressures.

Methods

Animal model. The heart from 250 to 300 g Sprague-Dawley rats was rapidly excised from the ether-anesthetized animal and was mounted on a perfusion apparatus. The ascending aorta was cannulated retrograde with polyethylene tubing (PE-280, 2.15 mm inner diameter, 3 cm length). The tip of the cannula was positioned just below the aortic valve. The other end of the cannula was connected to a T-stopcock with ports for pressure measurement and barium-gelatin infusion. An atriotomy was performed in the left atrial appendage and a short segment of polyethylene tubing was inserted across the mitral valve into the left ventricular cavity. This was done to vent the cavity of air and blood during the infusion. A barium-gelatin suspension was warmed to 40°C and was hand injected to the desired pressures through the aortic cannula. As the heart was filled, the left ventricular vent was clamped when barium-gelatin appeared within it. Three hearts were filled and fixed at 30 mm Hg, four at 70 mm Hg and four at 100 to 120 mm Hg. After the infusion, the heart was fixed in 3.7% buffered formaldehyde or 2.5% buffered glutaraldehyde for >2 weeks.

Silver impregnation. Subsequently, all hearts were sectioned into horizontal rings from apex to base, with the exception of one heart filled at 30 mm Hg, one filled at 70 mm Hg and two hearts filled at 100 mm Hg that were sectioned longitudinally parallel to the long axis of the ventricle. The horizontally sectioned hearts had the apical portions removed first (five hearts) by slicing the apex at the lower extent of the ventricular cavity. The cross-sectioned rings were cut from three levels: lower (mid to lower ventricle), midheart (midway from the apex to base) and upper (immediately below the anulus).

The remaining longitudinally sectioned hearts and all cross-sectioned specimens were mounted on a freezing microtome and were cut at 100 to 120 μm thickness; the apical pieces previously removed were sectioned en face. Floated sections then were stained with a modified del Rio Hortega's silver carbonate impregnation method, as described previously (5,11,12). This method impregnates cardiac skeletal framework connective tissue from relatively thick tendinous fibers down to the thinnest fibrils visible with the light microscope (5,8). The silver does not stain trichrome-positive scar tissue or impregnate annular or papillary muscle tendon tissue.

Tissue examination and quantitation. Impregnated tissues were examined and photographed with a Zeiss Photomicroscope III by both transmitted and polarized light. Phase optics or defocusing the substage condenser was employed to visualize sarcomeres for measurements. Representative photomicrographs were taken from all sectioned areas. Particular attention was paid to the interface between ventricular mural layers (where fiber orientation changed from longitudinal to oblique to cross sections), to the apical and basal orientation of connective tissue fibers and to the configuration of coiled fibers in relation to sarcomere length. All photomicrographs were examined by one of us (S.M.F.) without knowledge of the loading conditions.

For the purpose of measuring sarcomere length, a calibrated reticle with 0.01 mm line separation was photographed at all magnifications used in this study. A minimum of 15 (but generally 20 to 30) sarcomeres were counted over a defined distance measured either directly on the photographic slide or its projected image. The average sarcomere lengths were calculated by dividing the measured length from the calibration slides by the number of sarcomeres within that length. Average sarcomere lengths were determined at all levels of ventricular section (e.g., base, midwall and apex) and in regions of coiled, partially coiled and straightened fibers. No correction for fixation-induced tissue shrinkage or myocardial contracture was made because sarcomeres were compared with others in different regions of the same heart or between different hearts processed in an identical manner.

To determine wall thickness, sectioned midventricular rings from hearts fixed at the three different filling pressures were projected onto a screen at a calibrated magnification. Five equally spaced measurements perpendicular to the endocardium and epicardium, encompassing the longest and shortest wall thickness, were made on the projected image. Papillary muscles were not included in the measurements. A mean absolute value was obtained after correcting for magnification.

Statistics. Statistical comparison of sarcomere lengths at different cavity pressures was performed with a one-way analysis of variance, followed by Scheffe's test.

Results

Coiled perimysial fibers. The coiled perimysial fibers were progressively affected by increased ventricular cavity pressure, with straightening of the coiled configuration. At 30 mm Hg pressure, coils were heterogeneously affected with regions of straightening, partial coiling and tight coiling frequently in the same field (Fig. 1). Straightening was most apparent at the midventricular level, but it could be observed focally at all levels. At 70 mm Hg pressure, straightening was more generalized with less heterogeneity, but partially coiled fibers were noted focally (Fig. 2). Additionally, straightened fibers occasionally demonstrated deep bowlike dips (Fig. 2), as if they were too long for the fixed muscle length. At 100 mm Hg pressure there was essentially no heterogeneity, with

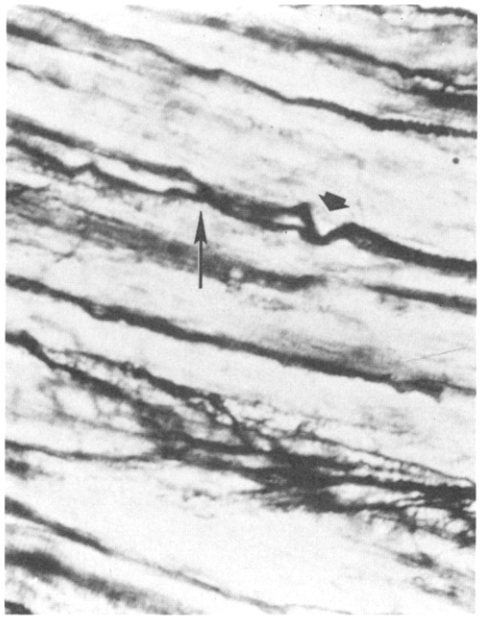

Figure 1. Section of mid left ventricle from a heart fixed at 30 mm Hg pressure shows numerous coiled perimysial fibers with variable coiling. Several tightly coiled fibers (**straight arrows**) and partially coiled fibers (**curved arrows**) can be seen in close proximity to each other within the same field (del Rio Hortega's stain; original magnification ×335, reduced by 25%).

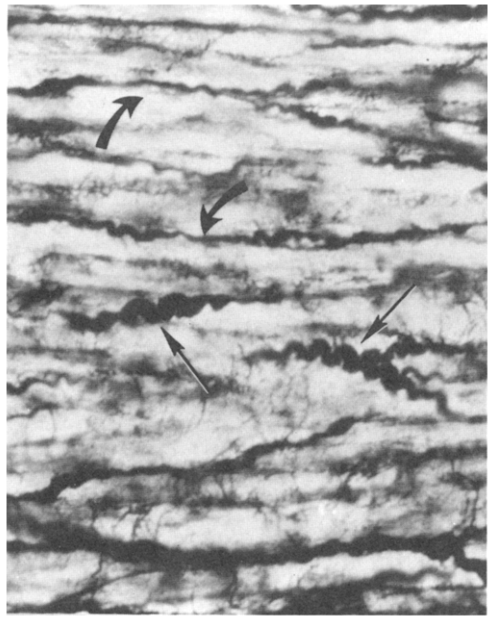

Figure 2. Section of left ventricle from a heart fixed at 70 mm Hg pressure shows predominantly straight coiled perimysial fibers. One fiber (**arrow**) shows some slight coiling whereas the adjacent fiber has a bowlike dip (**arrowhead**) suggestive of buckling after stretching and relaxation (del Rio Hortega's stain; original magnification ×65, reduced by 25%).

virtually all fibers straightened; the only exceptions were those at the anulus or those with rupture (see discussion to follow).

At the annular insertion, coils from ventricles filled up to 70 mm Hg generally maintained their springlike configuration, although occasionally with slight stretching. At 100 mm Hg ventricular pressure there was marked lateral displacement of coils at the anulus, with coil straightening within the inner 50% of the wall but maintenance of coiling in the subepicardium (Fig. 3). At the apex, coils came together in a knotlike mass equivalent to an "umbilicus" (Fig. 4). These coils were focally or completely straightened at all pressures, but no unraveling was observed, even at 100 mm Hg. The annular insertion and the apical interweaving of coils represent what we believe to be anchoring points for the coiled perimysial fibers at both ends of the ventricle.

At 100 mm Hg pressure some coils were noted to be disrupted. This disruption was observed in particular at the midventricular level and was associated with irregular looping and fraying of connective tissue fibers oriented parallel to myocytes (Fig. 5). This appearance was completely different from that associated with coil untethering; as rarely noted with artifactual tearing of these structures, they maintained their coiled configuration even when unattached at one end (Fig. 6). We also have noted maintenance of coiling after pronase digestion of heart muscle, in which only connective tissue structures are preserved in isolated fragments (unpublished observations). The loss of coiling with pronounced stretch and the preservation of coiling with artifactual tearing suggest that untethering of coils at one or both ends does not account for the straightening of these springlike structures; rather, marked stretch must lead to fiber damage that prevents recoiling.

Wall layers. The coiled perimysial fibers are arrayed in an apical to basal orientation where they run parallel to the myocytes. Thus there is a helical twisting of at least three layers of these fibers comparable with the longitudinal, oblique and horizontal orientation of the myocytes. As noted previously, the coils anchor at both ends of the ventricle, embedding themselves in the fibrous anulus at the base and knotting up at the apex. Therefore, the midventricle is the greatest distance from the anchoring points of these fibers, and may be most susceptible to bulging with increased cavity pressure. Although it is impossible to follow a single coiled fiber from one end of the ventricle to the other because of branching and movement out of the tissue section, it appears that these fibers are continuous within any given wall layer. With the ventricle fixed at high intracavity pressures, the coils straighten and coalign with each other and with the myocytes within an individual layer.

Pressures up to 70 mm Hg had little effect on the ventricular wall at the midventricular level; however, at 100 mm Hg the wall thickness was markedly attenuated. The mean mural thickness at the midwall was 1.53 mm at 30 mm

Figure 3. Section of left ventricular base in the region of the anulus (**starred**) from a heart fixed at 100 mm Hg pressure. In the inner wall (closest to the ventricular cavity) the coils are stretched and straightened (**straight arrows**). In the subepicardium, the fibers are predominantly coiled (**curved arrows**) (del Rio Hortega's stain; original magnification ×360, reduced by 25%).

Hg, 1.50 mm at 70 mm Hg and 0.71 mm at 100 mm Hg. At this latter pressure, struts and strutlike fibers between ventricular layers were stretched and frequently acutely angulated along the sarcolemma in contrast to their normal perpendicular orientation (Fig. 7). Focally, but particularly in the midventricle, connections between layers were torn, with the ragged ends still visibly attached to cell surfaces (Fig. 8). In these high pressure specimens, struts *within* each layer that join individual myocytes were intact and often slack (Fig. 9).

At the apex, in en face-sectioned specimens, the muscle layers and coiled perimysial fibers were observed to spiral down toward a central point where the "umbilicus" was located (Fig. 10). In high pressure hearts at 70 and 100 mm Hg, the orientation and angulation of the layers changed in comparison with those hearts filled at 30 mm Hg, but unraveling of the connective tissue was not observed.

Sarcomeres. In hearts fixed at either 30 or 70 mm Hg, sarcomeres measured within a range of 1.6 to 2.2 μm, with the exception of one midwall measurement of 2.3 μm in one heart fixed at 70 mm Hg. There was no difference in sarcomere length related either to the ventricular region sampled (e.g., base, midventricle or lower ventricle) or to the configuration of the coiled perimysial fibers (straightened, partially straightened or coiled). Some focal heterogeneity was observed but, in general, sarcomere length was maintained within these limits. Thus, although there appeared to be marked variability in coil stretch, such stretch induced by pressures up to 70 mm Hg did not have a comparable effect on sarcomere lengths (Table 1). As an example, measurements at the base of heart 1, fixed at 30 mm Hg, revealed identical sarcomere lengths of 1.8 μm in

Figure 4. Section of the apex (APEX) shows the ventricular cavity (**above**) appearing black because of the barium-gelatin mixture. In the outer wall a knotlike mass of straightened coiled fibers is seen between the **arrows** where the fibers come together in a central umbilicus. These fibers were straightened at all pressures used in this study (del Rio Hortega's stain; original magnification ×135, reduced by 25%).

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Figure 5. Midventricular section from a heart fixed at 100 mm Hg pressure. The coiled fibers are virtually all straight (**thick arrows**) and coaligned with the long axis of the myocytes. A looped fiber (**starred**) with a free, torn end (**thin arrow**) is present in this field. Several other looped fibers can be seen out of the focal plane (del Rio Hortega's stain; original magnification ×450, reduced by 25%).

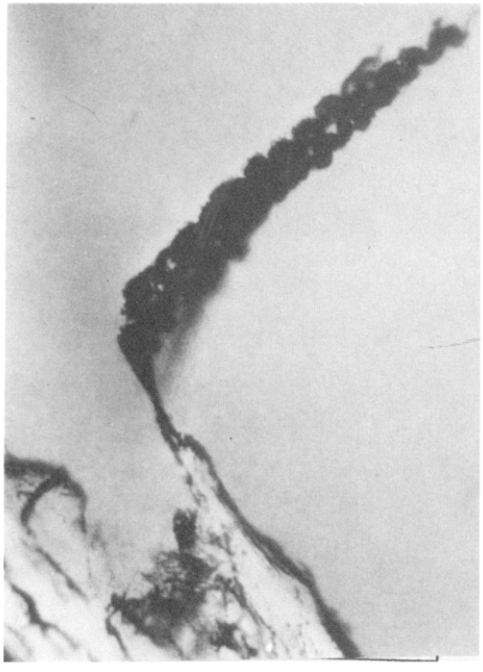


Figure 6. Several coiled perimysial fibers that were artifactually torn during sectioning lie free within the ventricular cavity with only partial attachment to the ventricular wall. The fibers maintain their tight coiling despite being untethered at one end (del Rio Hortega's stain; original magnification ×350, reduced by 25%).

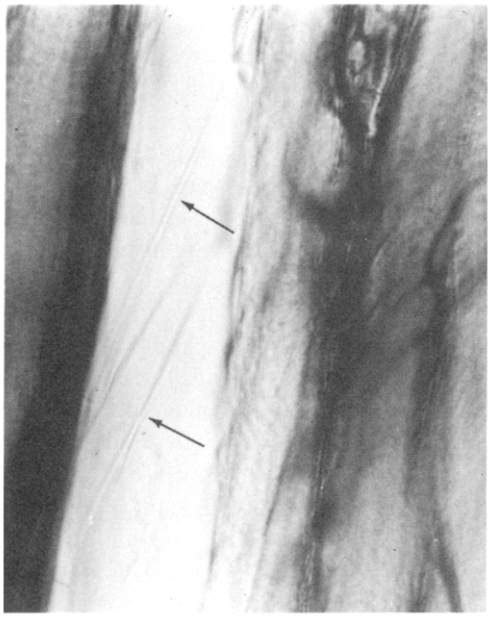
two separate regions, with coil stretch in one area 19% greater than in the other (0.50 versus 0.42 coils per unit length). These findings suggest that the coils absorb the effects of stretch before it is transmitted to myocytes, at least within the somewhat artificial conditions of these experiments.

At 100 mm Hg ventricular pressure, the average sarcomere lengths were stretched beyond 2.2 μm in all regions of the hearts sampled, with the exception of one midwall measurement of 2.1 μm. In both hearts, sarcomeres were measured up to 2.6 and 2.9 μm in association with coiled perimysial fiber tearing; similar measurements were also obtained without visible coil disruption (Table 1).

Discussion

Background. This study shows the effects of graded, increased passive intraventricular pressure on the organization, orientation and integrity of intrinsic myocardial connective tissue. We have previously shown (5,6) that epimysial connective tissue surrounding papillary muscles changes its configuration from a slack "cargo netlike" structure, to one where the fibers are relatively coaligned when the muscle is stretched and fixed at maximal length. We also recently demonstrated (9) the effects of passive stretch on papillary muscle coiled perimysial fibers and noted straightening of coils at 15% muscle stretch. Our papillary muscle

Figure 7. Several struts (**arrows**) at the interface between two mural layers of a ventricle fixed at 100 mm Hg pressure are markedly stretched and angulated relative to the sarcolemma of the longitudinally and obliquely oriented myocytes. Normally, struts are essentially perpendicular to the cell surfaces (del Rio Hortega's stain; original magnification ×1,400, reduced by 25%).



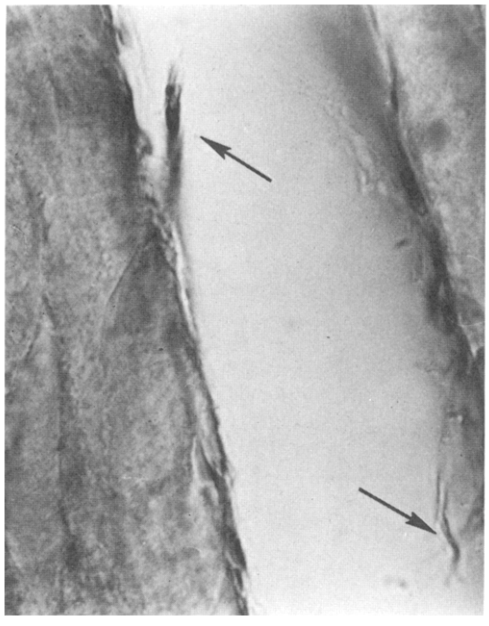


Figure 8. The ends of a torn strut (**arrows**) are present in the interstitial space between two mural layers in this section from the midventricle of a heart fixed at 100 mm Hg pressure (del Rio Hortega's stain; original magnification ×1,700, reduced by 25%).

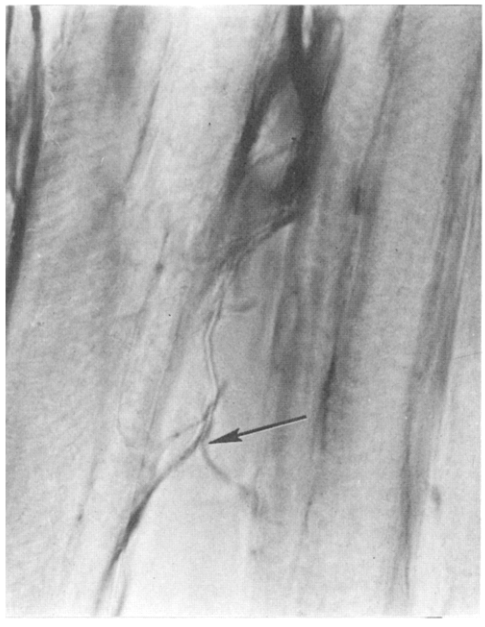


Figure 9. The interstitial space between longitudinally oriented myocytes within a mural layer from a heart fixed at 100 mm Hg pressure has struts (**arrow**) appearing intact but slack (del Rio Hortega's stain; original magnification ×1,700, reduced by 25%).

studies (9) revealed that 1) coiled perimysial fibers are located within the interstitial space and are oriented parallel to the long axis of myocytes; 2) they are interconnected to each other and to myocytes by strutlike fibers; 3) they are composed of triple helically wound fibers; and 4) they are embedded in the fibrous tendon of the muscle as an anchoring point. Beyond the belly of the muscle they extend into the ventricular wall at the attachment of the papillary muscle. Under conditions of zero load in well fixed hearts, coiled perimysial fibers in both the papillary muscle and ventricular wall are always in a tightly coiled configuration without areas of straightening.

Present observations. This study demonstrates that there are large numbers of these coiled perimysial fibers in all layers of the ventricular wall. They embed within the anulus at the base and they form an "umbilicus" or knotlike mass at the apex. Thus, common anchor points for the global collagen network occur at least at these two ends of the ventricle, and the fibers appear to be most compliant at the ventricular equator midway between the points of fixation. This organization of these long-coiled ventricular fibers, with anchoring points comparable with those of the papillary muscle tendon and the papillary muscle base, may have important mechanical implications not previously considered in analyses of ventricular function.

Increased intraventricular cavity pressure, at all levels studied, stretches the coiled perimysial fibers. At 30 mm Hg this effect was variable and frequently heterogeneous, whereas at the two higher pressures straightening was common. However, it was only at the highest pressures (100 to 120 mm Hg) that physical disruption of these fibers occurred, and it was only in these hearts that sarcomeres were markedly stretched. This finding supports our hypothesis that the coiled fibers may serve as buffers to prevent overstretching the myocytes and that this function is maintained up to the point where they lose their integrity. They therefore may have an important role in moderating the beat to beat changes that occur during normal cardiac function and in protecting the myocardium from overstretch during conditions associated with a high end-diastolic pressure or during regional asynergy. Whether they also serve any function in ventricular elastic recoil (7,13) will require additional study.

Potential methodologic problems. Caution must be taken in the interpretation of the sarcomere measurements of this study in comparison with those measured in contracting myocardium (14) or in myocardium studied with the electron microscope (15–17). The sarcomere measurements may be affected by fixation-induced tissue shrinkage, ventricular contracture and imprecision in determining length with the light microscope. We did not attempt to correct for shrinkage, contracture artifacts, or both, because we were interested in a comparison of sarcomeres relative to connective tissue morphology in the same heart or in other hearts fixed in an identical manner at the same pressure. The measurements cannot be used for comparison with the physiologic range of sarcomere lengths described in the classic studies by Sonnenblick and coworkers (15–17) in which they showed a close correlation between sarcomere length and pressure-

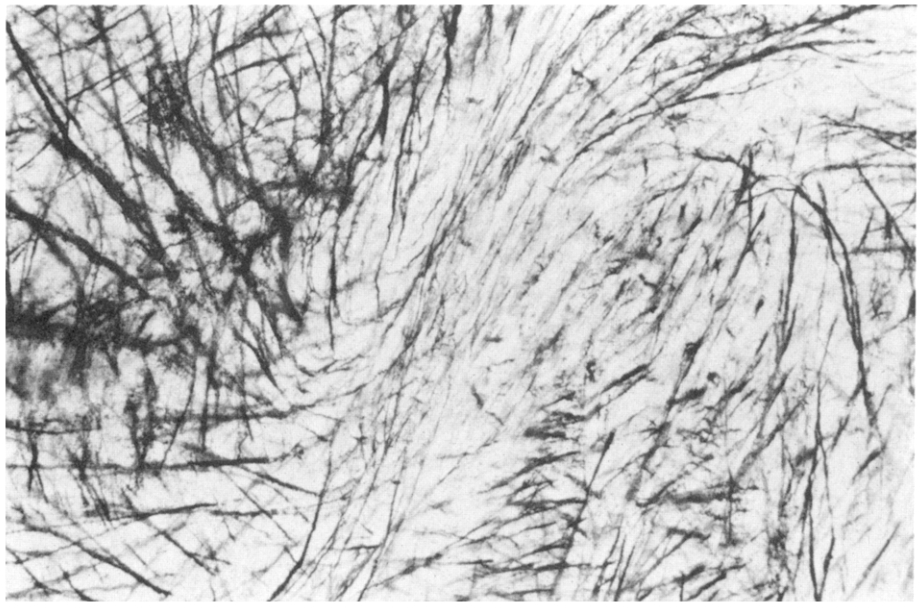


Figure 10. En face section of the ventricular apex from a heart fixed at 70 mm Hg pressure shows the orientation of the coiled perimysial fibers within the mural layers as they spiral toward the knotlike umbilical mass of fibers seen in Figure 4. At this pressure, the fibers show essentially no coiling (del Rio Hortega's stain; original magnification ×140, reduced by 25%).

volume curves of intact ventricles of dog and cat. The use of perfusion fixation and ultrastructural measurement with the latter studies probably led to a greater degree of precision.

Furthermore, the hearts in the present study were not fixed in diastole with potassium or in systole with calcium arrest; therefore, the determination of preloading or afterloading conditions before cavity filling may be problematic. We believe that the consistent observations and the gradation of changes as cavity pressure increased suggests that the loading conditions were comparable and probably simulated diastole. If fixation pressure was equivalent to diastolic pressure, then the high filling pressures at which fiber disruption occurred were above the physiologic range. However, these pressures were chosen specifically to perturb the connective tissue maximally to determine its adaptiye capacity up to and beyond physiologic levels, thereby allowing extrapolation to more natural conditions.

Table 1. Sarcomere Length in Pressure-Filled Hearts

Heart No.	Pressure (mm Hg)	Sarcomere Length (μm) Mean	Sarcomere Length (μm) Range	CPF Configuration
1	30	1.8 (7)*	1.6 to 2.0	Generally coiled
2	30	2.0 (4)	1.8 to 2.1	
3	70	1.9 (6)	1.8 to 2.1	Straight/focally
4	70	2.0 (3)	1.9 to 2.1	coiled
5	70	1.9 (7)	1.6 to 2.3	
6	100	2.4 (2)	2.3 to 2.6	Straight/torn
7	100	2.6 (4)	2.1 to 2.9	

Group†		Mean Length (μm) (±SD)	p Value
1	(30 mm Hg)	1.9 ± 0.13	I vs. II; NS
2	(70 mm Hg)	2.0 ± 0.04	I vs. III; <0.01
3	(100 mm Hg)	2.5 ± 0.12	II vs. III; <0.01

*Numbers in parentheses represent the number of separate measurements from different areas of myocardium. †For purposes of statistical analysis, sarcomere lengths from all hearts at the same cavity pressure were grouped together. CPF = coiled perimysial fiber.

Other connective tissue components. In addition to observations on coiled perimysial fiber morphology in relation to cavity expansion, we also observed profound changes in other connective tissue components associated with mural thinning at high pressure. The stretching and rupturing of interlayer connective tissue fibers permit the slippage of mural layers relative to each other. The wall-thinning characteristic of myopathic hearts with a large end-diastolic volume and high cavity pressures may be a result of such slippage associated with connective tissue disruption. At the highest pressures in this study, the midventricular wall was <50% the thickness of the wall in hearts fixed at 30 and 70 mm Hg (0.71 versus 1.50 and 1.53 mm, respectively). Because there was only approximately a 25% increase in sarcomere length at 100 mm Hg pressure, wall layer slippage must account for a major portion of the mural thinning. Further support for this hypothesis is apparent from the apical segments examined in this study, where the layers were noted to "unscrew" with increased cavity pressure.

It is of interest that the configuration and orientation of the connective tissue at the base and apex differed from those elsewhere in hearts fixed at 100 mm Hg cavity pressure. At the two ends of the ventricle the coiled perimysial fibers were relatively fixed and not affected by pressure uniformly; at the fibrous anulus they were coiled and splayed outward in the subepicardium and straightened only in the inner wall, whereas at the apex the umbilical knot of fibers remained relatively intact. The pattern seen at the basal attachment, apparent only in the acutely expanded ventri-

cles of this study, may represent a lesion seen in chronically dilated hearts in which annular dilation occurs in association with valvular insufficiency.

Connective tissue and cardiac dysfunction. Finally, there have been recent observations of 1) intrinsic connective tissue destruction in ischemic stunned myocardium associated with mural thinning and contractile dysfunction (18), 2) disruption of connective tissue in early ischemic necrosis (19) and, 3) in necrotic myocardium, disruption associated with infarct expansion and rupture (20). These findings raise the possibility that additional unsuspected perturbations of connective tissue may be related to other types of unexplained heart disease. Damage to connective tissue, either mechanical or enzymatic, in the absence of concomitant injury to myocardium could theoretically produce ventricular dysfunction. Such abnormalities, which have yet to be identified, may account for those cardiomyopathies in which the degree of morphologic damage (e.g., myocyte necrosis and replacement fibrosis) does not appear sufficient to account for the contractile dysfunction. Even in those cardiomyopathies with damage, abnormalities of intrinsic connective tissue may amplify the extent of myocyte loss and contribute to further ventricular dysfunction. This has been observed recently in the cardiomyopathic Syrian hamster (21) and may be a more frequent occurrence than suspected. Clearly, further studies of intrinsic connective tissue in clinical heart disease are warranted by the observations made in this study and by the data accumulated in recent investigations of normal and diseased hearts.

Conclusions. Our observations indicate that there are profound alterations in connective tissue in ventricles subjected to relatively high cavity pressures with concomitant changes in ventricular mural layers. These findings suggest an important role for this connective tissue in normal and abnormal hearts.

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